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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,629	07/05/2001	Shuang Liu	PH-7176	5136

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EXAMINER	
WANG, SHENGJUN	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,629	LIU ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-92 is/are pending in the application.

4a) Of the above claim(s) 1-18,23-29,34 and 40-92 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 19-22,30-33,35-39 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the remand of the Board of Patent Appeals and Interferences issued on August 31, 2005, PROSECUTION IS HEREBY REOPENED. An office action is set forth below.

Restriction and Species Election

Claims 1-18, 40-92 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, Claims 23-29, 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

1. Applicant's election with traverse of invention group V, claims 19-38. Applicant elected trihydroxy benzoic acid as the stabilizer. Applicant elected RI is 90Y; Ch is chelator; Ln is a linking group; BM is a peptide; and x is 2 as to the radiopharmaceutical compounds, with compound A disclosed at page 68 as a particular example. ***Upon reconsideration, the species election requirement for the radiopharmaceutical compounds regarding to RI, Ch, Ln, BM, and x is herein with drawn*** as the claims are not particularly limited to any species of compounds which comprising a metal chelator linked to a peptide or peptidomimetic, by a linker. The claims have been examined insofar as they read on compounds comprising a metal chelator moiety, a linker, and a peptide or peptidomimetic.

2. Claimed invention. It is noted that the specification defines a "peptide" as " a linear compound having two or more amino acids... that are linked by means of peptide bond." Page 26 of the specification. It is also noted that in illustrating the invention, cyclo-peptide are used as examples See, pages 65-72. Applicants also elected compound A disclosed at page 67 as the

peptide compound. Compound A is a cyclo-peptide compound. Further, the claims would read on any other peptidomimetics. The application defines peptidomimetics or pseudopeptide as a compound which mimics the structure of an amino acid residue or a peptide, for example, by using linking groups other than amide linkages between the peptide mimetic and an amino acid residue (pseudopeptide bonds) and/or by using non-amino acid substituents and/or a modified amino acid residue. A pseudopeptide residue means that portion of a pseudopeptide or peptidomimetic that is present in a peptide. Page 26 of the specification. Therefore, "peptide" or "linear compound" herein is interpretated as read on cyclo-peptide or any peptidomimetics in view of the specification and applicants' election of a cyclo-peptide compound as the "peptide"

3. As an outside matter, it is noted that groups I-IV require the present of (1) a substituted monohydroxyl aromatic compound; (2) a substituted dihydroxyl aromatic compound, in which the two hydroxyl groups are not adjacent to each other; (3) a substituted monohydroxyl-mononmino aromatic compound, in which the hydroxyl group and amino group are not adjacent to each other; or (4) an ortho, meta, or para aminobenzioc acid. See the reasoning of distinct in the restriction requirements mailed December 12, 2002.

Double Patent Rejetions

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 19-22, 30-33, 35-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 28-30 of U.S. Patent No. 6537520 in view of Vanderheyden et al. (US 5,679,318) and in further view of Nippon oils (JP 56144060).

'520 claims a pharmaceutical composition, or kit, comprising the radionuclide herein. Particularly, the compound A herein disclosed and elected by applicants is claimed. See, claim 30, the compound (r) (column 158, lines 34-36), ^{90}Y is one of the metal claimed. See claim 26. '520 does not expressly claims the stabilizers in the composition or kit. However, Vanderheyden et al. teaches that therapeutical radionuclide compositions generally require the presence of stabilizer. The stabilizer provides enhanced long term stability. One of the well know stabilizer is antioxidant. See, particularly, the abstract. Examples of antioxidants are gentisic acid, or its derivatives, or functionally similar compounds which are suitable for in vivo human administration (column 10, lines 43-58). The amount of stabilizer applied is about 1 mg/ml to 15 mg/ml. (column 10, line 66 to column 11, line 8). The radionuclide may be 90Y (column 5, lines 19-34). Nippon oils teaches gallic acid (3,4,5 trihydroxy benzoic acid, the first trihydroxy benzoic acid recited in claim 22 herein) is a known antioxidant, and are suitable for human consumption. See, particularly, the abstract.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to add antioxidants to the composition in '550 as stabilizers. The employment of the particular antioxidants, e.g., gallic acid and/or gentisic acid is

seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). The employment of more than one antioxidants, e.g., gallic acid and gentisic acid, would have been obvious because it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is a combination of two known antioxidants sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069.

Claim Rejections 35 U.S.C. 103

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 19-22, 30-33, 35-39 are rejected under 35 U.S.C. 103(a) as being obvious over Rajopadhye et al (US 6537520) in view of Vanderheyden et al. (US 5,679,318) and in further view of Nippon oils (JP 56144060).

9. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

10. Rajopadhye et al teaches a pharmaceutical composition, or kit, comprising the radionuclide herein. See, the abstract, and the claims. Claim 26 particularly recite 90Y, the compound A herein disclosed and elected by applicants are specifically recited. See, claim 30, the compound (r) (column 158, lines 34-36),

11. Rajopadhye et al does not expressly teach stabilizers in the composition or kit.

12. However, Vanderheyden et al. teaches that therapeutical radionuclide compositions generally require the presence of stabilizer. The stabilizer provides enhanced long-term stability. One of the well know stabilizer is antioxidant. See, particularly, the abstract. Examples of antioxidants are gentisic acid, or its derivatives, or functionally similar compounds which are suitable for in vivo human administration (column 10, lines 43-58). The amount of stabilizer applied is about 1 mg/ml to 15 mg/ml. (column 10, line 66 to column 11, line 8). The radionuclide may be 90Y (column 5, lines 19-34). Nippon oils teaches gallic acid (3,4,5 trihydroxy benzoic acid, the first trihydroxy benzoic acid recited in claim 22) is a known antioxidant, and are suitable for human consumption. See, particularly, the abstract.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to add antioxidants to the composition in '550 as stabilizers. The employment of the particular antioxidants, e.g., gallic acid and/or gentisic acid is seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). The employment of more than one antioxidants, e.g., gallic acid and gentisic acid, would have been obvious because it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is a combination of two known antioxidants sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069.

13. Claims 19-22, 30, 31, 33, 35-39 are rejected under 35 U.S.C. 103(a) as being obvious over Sworin et al. (5,750,088), in view of Vanderheyden et al. (US 5,679,318) and in further view of Nippon oils (JP 56144060).

14. Sworin et al., or Toner et al. teaches radionuclide conjugates wherein the radionuclide attached to a peptide, or protein, or peptidomimetic moiety through a metal chelator moiety. Particularly, Sworin et al. teach a stable radiopharmaceutical for imaging agent. The compounds comprising a hydrozne (metal chelator) linked to a peptide moiety. The radio active metals include ^{99m}Tc, ^{186}Re, ^{188} Re. See, particularly, the abstract, column 37, lines 46-58. and the claims in Sworn et al.

15. The primary references do not teach expressly adding stabilizers, such as gallic acid, in the radionuclide conjugate composition.

16. However, Vanderheyden et al. teaches that therapeutical radionuclide compositions generally require the presence of stabilizer. The stabilizer provides enhanced long-term stability. One of the well know stabilizer is antioxidant. See, particularly, the abstract. Examples of antioxidants are gentisic acid, or its derivatives, or functionally similar compounds which are suitable for in vivo human administration (column 10, lines 43-58). The amount of stabilizer applied is about 1 mg/ml to 15 mg/ml. (column 10, line 66 to column 11, line 8). The radionuclide may be ^{90}Y, ^{186}Re, or ^{188} Re (column 5, lines 19-34). Nippon oils teaches gallic acid (3,4,5 trihydroxy benzoic acid, the first trihydroxy benzoic acid recited in claim 22) is a known antioxidant, and are suitable for human consumption. See, particularly, the abstract.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to add antioxidants to the radionuclide conjugate

compositions disclosed in the primary references as stabilizers. The employment of the particular antioxidants, e.g., gallic acid and/or gentisic acid is seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). The employment of more than one antioxidants, e.g., gallic acid and gentisic acid, would have been obvious because it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is a combination of two known antioxidants sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069.

17. Claims 19-22, 30-33, 35-39 are rejected under 35 U.S.C. 103(a) as being obvious over Toner et al. (US 5,707,603), in view of Vanderheyden et al. (US 5,679,318) and in further view of Nippon oils (JP 56144060).

18. Toner et al. teaches radionuclide conjugates wherein the radionuclide attached to a peptide, or protein, or peptidomimetic moiety through a metal chelator moiety. See the abstract and the claims. Particularly, Toner et al teaches a complex (metal chelator) linked to an immunoreactive group through an amino group, or amino containing moiety. See, e.g., compounds 20-24 in columns 19-22. The radioactive metals include ^{90}Y (claims 15, 21). The immunoreactive group may be peptide (claim 12).

19. The primary references do not teach expressly adding stabilizers, such as gallic acid, in the radionuclide conjugate composition.

20. However, Vanderheyden et al. teaches that therapeutical radionuclide compositions generally require the presence of stabilizer. The stabilizer provides enhanced long-term stability. One of the well know stabilizer is antioxidant. See, particularly, the abstract. Examples of antioxidants are gentisic acid, or its derivatives, or functionally similar compounds which are suitable for in vivo human administration (column 10, lines 43-58). The amount of stabilizer applied is about 1 mg/ml to 15 mg/ml. (column 10, line 66 to column 11, line 8). The radionuclide may be 90Y (column 5, lines 19-34). Nippon oils teaches gallic acid (3,4,5 trihydroxy benzoic acid, the first trihydroxy benzoic acid recited in claim 22) is a known antioxidant, and are suitable for human consumption. See, particularly, the abstract.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to add antioxidants to the radionuclide conjugate compositions disclosed in the primary references as stabilizers. The employment of the particular antioxidants, e.g., gallic acid and/or gentisic acid is seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). The employment of more than one antioxidants, e.g., gallic acid and gentisic acid, would have been obvious because it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, the claimed invention which is a combination of two known antioxidants sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069.

Response to the Arguments

Appellants argue that the double Patenting rejections over '520 are improper because references other than the '520 patent were cited in the rejections. The arguments have been fully considered, but are not persuasive. It should be understood that secondary references are permissible in the double patenting rejections. See, MPEP 8.04.

1. In response to appellants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Particularly, Vanderheyden et al. teach a specific dihydroxy benzoic acid, and its derivatives or functionally similar compounds, for use as antioxidants. The teaching would have fairly suggested that trihydroxy benzoic acid would be similarly useful. Nippon Oil and Fats is cited to show the trihydroxy benzoic acid is a known antioxidant in the art. Therefore, considering the cited references as a whole, the employment of trihydroxy benzoic acid as a stabilizer in radioactive therapeutical composition would have been obvious to one of ordinary skill in the art. The examiner has noted that appellant meticulously excluded the compounds particularly disclosed by Vanderheyden et al. from the claimed antioxidants herein. Such negative limitations are sufficient to avoid a clear anticipation by the prior art, but are not persuasive to the obvious rejections set forth above. The scope of antioxidants suggested by Vanderheyden et al. is much larger than those three specific compounds. Vanderheyden et al. teach the stabilizers used in radioactive composition may be ascorbic acid, gentisic acid, reductic acid, and their derivatives, and functionally similar compounds. (col. 10, line 43-50). In view of the teaching by Vanderheyden et al, and the fact that

gallic acid is a structural derivative of gentisic acid (with one more hydroxyl group at the aromatic ring), and is a known antioxidant, one of ordinary skill in the art would have seen the employment of gallic acid in a radio active composition as an obvious variation to gentisic acid. Further, there is no evidence on the record showing the antioxidants herein recited are any different functionally from those disclosed by Vanderheyden et al.

In response to appellants' arguments that Nippon Oil and Fats is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Nippon oil is reasonably pertinent to the particular problem with which the applicant was concerned, i.e., non-toxic antioxidant suitable for human consumption.

Appellants further contend that Nippon Oils and Fats requires the combination of ascorbic acid and gentisic acid, and therefore, teach away from the instant claims.

The arguments have been fully considered but are not persuasive. It is noted that the features upon which applicant relies (i.e., no combination with ascorbic acid) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, the rejections are based on the combination of the cited references, Nippon oil was cited to show that the trihydroxy benzoic acid recited herein is known in the art as an antioxidant.

The above rejections are essentially the same as those on the record, but to address the issues raised by the Board of Patent Appeals and Interferences. No new ground of rejections have been applied.

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHENGJUN WANG/
PRIMARY EXAMINER

Shengjun Wang
Primary Examiner
Art Unit 1617